Alcohol and Breast Cancer

The lifetime risk for breast cancer among U.S. women is estimated to be as high as one in eight (Feuer et al. 1993). Over the past two decades, interest in identifying dietary factors that influence breast cancer has been high, and evidence from a number of epidemiologic studies suggests that alcohol consumption, particularly at high levels, can increase breast cancer risk. Whether a woman consumes wine, beer, or distilled spirits is unimportant; it is the amount she drinks that appears to be critical. Research has begun to shed light on how alcohol could promote breast cancer growth and to identify several factors that influence alcohol's impact on this disease.

The relationship between breast cancer risk and alcohol intake was first noted in the 1970's among women participating in the third National Cancer Survey (Williams and Horm 1977). Approximately 50 epidemiologic studies scrutinizing this association have followed. In addition, combined data from many of these studies have been evaluated using a statistical method called "meta-analysis" (Holman et al. 1996; Longnecker 1994; Longnecker et al. 1988). One such analysis of six case-control studies (comparing women with breast cancer with matched women with no breast cancer) showed that women who drank three or more alcoholic beverages per day (or 40 grams of alcohol, with about 13 grams in a standard drink) had a 69 percent higher risk of getting breast cancer compared with nondrinkers (Howe et al. 1991). A separate analysis of six prospective studies (following healthy women over time, recording their alcohol consumption, and noting which women developed breast cancer) showed that those who had two to four drinks per day (30 to 60 grams of alcohol) had a 41 percent greater risk of getting breast cancer than those who did not drink (Smith-Warner et al. 1998). Over a range of one to six drinks per day, the relationship of alcohol to breast cancer was linear—the more women drank, the higher their risk compared with nondrinkers.

The findings of the meta-analyses and of a majority of these epidemiologic investigations, including two recent large case-control and cohort reports (which study a population rather than selected women with breast cancer), point to an increase in breast cancer risk associated with alcohol consumption (Bowlin et al. 1997; Longnecker 1995; Thun et al. 1997; and World Cancer Research Fund Panel 1997).

Controversy remains over the interpretation of these studies, however (Katsouyanni et al. 1994; Plant 1992; Rosenberg et al. 1993; Roth and Levy 1995; Schatzkin and Longnecker 1994). For epidemiologists, the actual numerical association between alcohol and breast cancer risk is considered relatively modest. In addition, some studies found no link between high alcohol intake and breast cancer risk (Freudenheim et al. 1995; Rohan et al. 1993; Smith et al. 1994).

Nonetheless, substantial evidence, obtained from populations in several countries, suggests that breast cancer risk is elevated for women consuming high levels of alcohol (more than three drinks per day) compared with abstainers. Some studies report a dose-response relationship—drinking larger quantities of alcohol leads to more cases of breast cancer (Longnecker 1994). There is evidence that consuming as few as one to two drinks per day can increase risk, though to a lesser degree than the moderate risk seen with three daily drinks (Longnecker et al. 1988; Smith-Warner et al. 1998). Not all studies have detected this association, however (Zhang et al. 1999).

Scientists have identified plausible biological mechanisms for alcohol's action, an important piece of the puzzle in establishing a connection between alcohol and breast cancer. In many investigations, an effect of alcohol has been

demonstrated after age, family predisposition, and other known dietary and reproductive risk factors have been taken into account. At this time, no other confounding factors have been identified that can reasonably explain the enhancing effect of alcohol consumption on breast cancer risk.

Age, Genetics, and Other Risk Factors

Although no other factors can account for the increased risk associated with alcohol noted in some studies, scientists are investigating other physiologic characteristics of individual women to determine their effect, if any, on alcohol-related risk. For example, although early studies linked alcohol consumed at younger ages with increased breast cancer risk (Harvey et al. 1987; van't Veer et al. 1989), more recent research has found a stronger relationship with risk for recent drinking (Holmberg et al. 1995; Longnecker et al. 1995*a*) or lifetime alcohol intake (Longnecker et al. 1995*b*).

A woman's genetic makeup also may play a role in her susceptibility to alcohol-related breast cancer. For example, a report by Freudenheim et al. (1997) suggests that genetic variations that reduce the effectiveness of the alcohol-metabolizing enzyme alcohol dehydrogenase are linked to an increased risk of breast cancer for premenopausal women who drink heavily. Other physiologic characteristics may influence alcohol-related breast cancer risk. Some, but not all, reports find that thin or lean women have higher risk associated with drinking compared with heavier women (Gapstur et al. 1992). Although there are a number of risk factors for breast cancer other than alcohol, drinking raises breast cancer risk even after age, family history of breast cancer, and other known dietary and reproductive risk factors are adjusted for.

Menopausal Status and Hormones

Research findings suggest a role for alcohol in breast cancer risk in both pre- and postmenopausal women. Several studies report that the risk of premenopausal breast cancer was elevated for women consuming alcohol (Friedenreich et al. 1993; Swanson et al. 1997; Viel et al. 1997). One investigation found this effect to be most apparent for women with advanced breast cancer (Swanson et al. 1997).

In the only study to examine premenopausal bilateral breast cancer (characterized by strong family predisposition), alcohol consumption increased risk (Haile et al. 1996). Other studies showed risk increases for postmenopausal breast cancer (Gapstur et al. 1992; Holmberg et al. 1995; van den Brandt et al. 1995). Still others found that alcohol consumption increases risk for both pre- and postmenopausal breast cancer (Bowlin et al. 1997; Longnecker et al. 1995*a*).

Many postmenopausal women take estrogen as hormone replacement therapy (HRT) to prevent heart disease and osteoporosis and to alleviate the symptoms of menopause. Alcohol use by women receiving HRT may increase risk (Gapstur et al. 1992; Zumoff 1997), although the data are not entirely consistent (Friedenreich et al. 1993).

Breast tumors are evaluated to see whether they contain docking sites, or receptors, on the cell surface for the hormones estrogen and progesterone. This information affects a person's treatment choices and prognosis. The degree to which alcohol raises breast cancer risk—and interacts with other factors such as HRT use to do so—may depend on the estrogen or progesterone receptor status of the breast tumor. One study found that alcohol increased risk for estrogen receptor-negative and progesterone receptor-negative tumors (to a greater extent than the two other types of receptor tumor subtypes) in women who had taken HRT and consumed 4.0 grams or more of alcohol (about a third of a standard drink) per day compared with abstainers who never used HRT (Gapstur et al. 1995). In contrast, a second study showed that the risk for women with estrogen receptor-positive tumors increased as alcohol consumption increased (Nasca et al. 1994). Additional research in this area may both clarify alcohol's interaction with receptors and other health factors and provide information on the mechanisms behind the effect.

Mechanisms of Alcohol-Related Breast Cancer

An important consideration in evaluating the credibility of the alcohol-breast cancer relationship is whether plausible biological mechanisms can be identified. Among the areas scientists have investigated in human studies are alcohol's potential to affect hormone levels, to cause changes in breast tissue, and to influence overall nutrition.

Hormones

Cumulative lifetime exposure to estrogen is considered an important contributor to breast cancer risk (Bernstein and Ross 1993; Toniolo 1997). A number of studies have examined whether alcohol raises estrogen levels in pre- and postmenopausal women. Although some studies report such an effect, the evidence is not conclusive that alcohol raises estrogen levels (Longnecker and Tseng 1998; Purohit 1998).

The question remains important and relevant to breast cancer, however. Some tissues, such as adipose or fat tissue, can produce estrogens from androgens—the "male" sex hormones that include testosterone, androstenedione, and dehydroepiandrosterone sulfate. Blood androgen levels have been shown to increase in premenopausal women who drink (Dorgan et al. 1994; Eriksson et al. 1994; Reichman et al. 1993). For example, blood androstenedione levels in women who consumed moderate amounts of alcohol (0.22 to 0.99 ounces per day, equivalent to less than one drink to up to two drinks) were 27.4 percent higher than in abstainers (Dorgan et al. 1994).

Alcohol intake may also increase exposure to natural or endogenous estrogen through changes in the menstrual cycle. Researchers observed that premenopausal women who drank moderate amounts of alcohol had more regular cycles and fewer long cycles than nondrinkers did (Cooper et al. 1996). This change in cycles would be expected to increase exposure to estrogen during the premenopausal years.

Other studies show that women on HRT who drink alcohol have significantly higher circulating estradiol and prolactin levels than women on HRT who do not drink (Ginsburg et al. 1995*a*,*b*). In a report by Ginsburg et al. (1996), women who drank 0.7 grams of alcohol per kilogram of body weight (two to three drinks for a 120-lb woman) on consecutive days rapidly exhibited a threefold increase in circulating estradiol concentrations compared with abstainers. However, there was no significant increase in the women who drank alcohol but were not on HRT.

Some alcoholic beverages, like bourbon and whiskey, contain compounds called phytoestrogens. These plant products have chemical structures that differ from endogenous estrogens but appear to have similar effects. Postmenopausal women who were given an extract of bourbon that contained no alcohol had a significant decrease in the blood levels of two hormones involved in regulating the menstrual cycle (luteinizing hormone and follicle-stimulating hormone) and a significant increase in prolactin (a hormone capable of supporting tumor growth) (Gavaler 1993).

Also noteworthy is a report that blood levels of the reactive alcohol metabolite acetaldehyde are significantly elevated during the high-estradiol phase of the menstrual cycle of women who drink alcohol and in women who drink and use synthetic estrogens (Eriksson et al. 1996).

Additional research is needed to clarify whether alcohol's effect on estrogens and androgens in women is consistently positive and of sufficient magnitude to contribute to the alcohol's ability to raise breast cancer risk.

Mammary Gland Tissue

Alcohol may alter the normal architecture of the breast. The relationship between the proportion of breast volume occupied by densities (found on mammography) and breast cancer risk is well established (Warner et al. 1992). Some, but not all, observational studies have reported that

women who drank alcohol had more areas within the breast occupied by these mammographic densities (Boyd et al. 1989; Funkhouser et al. 1993; Herrington et al. 1993). Additional studies are needed to establish the consistency and magnitude of any increase in mammographic parenchymal densities associated with alcohol intake, as well as to determine why and how these changes occur.

Nutrition

Alcohol consumption may influence food choices and disturb the body's use of essential nutrients. Several dietary factors have been linked to breast cancer risk (Hunter and Willett 1996). In particular, it has been reported that women who consume the lowest quantities of fruits and vegetables are at increased risk for breast cancer (Freudenheim et al. 1996). Women who consume alcohol, especially in higher quantities, have been reported to eat fewer fruits and vegetables (Millen et al. 1996; Serdula et al. 1996) and less beta-carotene (D'Avanzo et al. 1997). Alcohol consumption also has been associated with decreased blood concentrations of beta-carotene, lutein/zeaxanthin, and vitamin C, food components thought to help prevent cancer (Drewnowski et al. 1997; Forman et al. 1995). Therefore, part of alcohol's effect on breast cancer risk may be through decreased intake or impaired use of nutrients that may be capable of reducing cancer risk.

Animal Models of Alcohol and Breast Cancer

Investigators have used animal models to explore the relationship between alcohol intake and breast cancer (reviewed in Singletary 1997). Generally, three types of models have been used: spontaneous tumor development, chemically induced tumor development, and implantation of cancer cells. The results to date have been inconsistent, partly due to the small number of studies and the wide variety of experimental conditions, including the timing, manner, and dose in which the alcohol was administered; the use and dosage of cancer-causing agents or carcinogens; and dietary composition (Singletary 1997).

For example, in the rodent spontaneous mammary tumor model, only two of six published experiments showed enhancement of mammary tumor development for animals fed alcohol-containing diets compared with controls (Hackney et al. 1992; Holmberg and Ekström 1995; Schrauzer et al. 1979, 1982).

The chemically induced rodent mammary tumor model can be used to examine the effect of alcohol on specific stages in the cancer process. Alcohol provided to animals prior to or during administration of a carcinogen would be expected to influence the early or initiation stage of cancer development, whereas alcohol provided after carcinogen dosing would influence later steps in carcinogenesis, the promotion stage. In studies in which alcohol was fed to animals during both the initiation and promotion stages, development of chemically induced mammary tumors was not enhanced (McDermott et al. 1992; Rogers and Conner 1990). However, there was evidence of an enhancing effect when alcohol was provided during either the initiation or promotion stage (Grubbs et al. 1988; Singletary et al. 1991, 1995), although intermediate levels of alcohol were more effective than high levels in promoting tumors. In five experiments, alcohol fed to female rats during the initiation stage increased mammary tumor development (Grubbs et al. 1988; Singletary et al. 1991, 1995), and in two experiments, alcohol stimulated the promotion stage of mammary tumorigenesis compared with controls (Singletary et al. 1991, 1995). However, a typical dose-response relationship was not observed. In other words, mammary tumor development was significantly increased for animals fed intermediate (15 to 20 percent of calories) but not high (30 percent of calories) levels of alcohol (Singletary et al. 1991, 1995).

Alcohol may be capable of enhancing the progression of cancer as well. Increased metastasis (proliferation beyond the site of origin) of implanted breast cancer cells was observed for rats given alcohol in a liquid diet (Yirmiya et al. 1992).

Tumor Initiation. Several mechanisms have been proposed to explain the ability of alcohol to

initiate cancers in laboratory animals in different organs, including the breast (Garro and Lieber 1990; Rogers and Conner 1991; Seitz and Simanowski 1988). Although alcohol is not a genotoxic or directly deoxyribonucleic acid (DNA)-altering carcinogen, it can act as a cocarcinogen by influencing processes in the body associated with the initiation and promotion stages of carcinogenesis.

For example, alcohol induces the expression of select cytochrome P450's, a class of alcohol-metabolizing enzymes that can activate various carcinogens. Alcohol may also impair the liver's ability to clear certain carcinogens from the body, leaving the cancer-causing compounds to circulate among tissues such as the breast (Anderson et al. 1995).

Alcohol and its highly reactive metabolite, acetaldehyde, also have been linked to the body's inability to repair carcinogen-induced DNA damage (Espina et al. 1988). If left unrepaired, damage to critical regions of DNA in breast cells could lead to mutations and the subsequent initiation of cancer. Thus, in addition to stimulating carcinogens to do their damage, alcohol may inhibit the ability of some cells to detoxify and eliminate carcinogens. Finally, in studies of female rats, alcohol consumption was associated with the growth of more mammary gland terminal end buds, structures that have greater susceptibility to carcinogen-induced DNA damage than do other mammary gland structures, providing another possible contributing mechanism for cancer vulnerability (Singletary and McNary 1992).

Alcohol influences factors in the cell nucleus that regulate the expression of genes in the DNA. This feature of alcohol's action can have diverse effects, depending on the genes involved. For example, alcohol has demonstrated effects on nuclear factor kappa B, a factor that modulates the transcription of DNA to ribonucleic acid in the cell nucleus, a key step in protein synthesis and, thus, the expression of genes (Zakhari 1996). How alcohol alters gene expression—with effects that may include the promotion of cancer—is an important area for continued research.

Tumor Promotion. Alcohol intake may stimulate the second, or promotion, stage of tumor development by several possible mechanisms. Alcohol consumption has been associated with increased mammary gland cell multiplication in female rats treated with a breast carcinogen (Singletary and McNary 1994). The rate of cell proliferation is believed to be one of several important factors determining risk for cancer (Preston-Martin et al. 1990). When rodents are fed alcohol, their levels of circulating prolactin—a hormone that can stimulate the growth of breast tissue—increase (Dees and Kozlowski 1984).

Reactive oxygen species, highly reactive molecular fragments that are a by-product of alcohol metabolism, can harm cells and contribute to tumor promotion (Nordmann et al. 1990). Alcohol intake also decreases the immune system's ability to detect and destroy cancer cells (Yirmiya and Taylor 1993). This may be an important factor in explaining why breast cancer metastasis is enhanced in alcohol-consuming rats.

In Closing

Epidemiologic studies provide substantial support that breast cancer risk is increased for women consuming alcoholic beverages compared with abstainers. This effect is modest in magnitude and is not restricted to one type of alcoholic beverage. The risk is most pronounced at high intakes of alcohol. Increased exposure to estrogens and androgens with alcohol consumption is one plausible—but as yet unconfirmed—biological mechanism to explain alcohol's effect on breast cancer risk. To clarify alcohol's role in enhancing susceptibility to breast cancer, further research is needed in a number of areas, including specific drinking patterns, body mass index, dietary factors, family history of breast cancer, use of HRT, tumor hormone receptor status, and immune function status. Information gathered from animal studies is less compelling but nonetheless provides evidence that alcohol

may act as a weak cocarcinogen and weak breast tumor promoter. These actions in animals may be explained in part by alcohol's effect on induction of cancer-promoting biochemical pathways, circulating hormone levels, structural development of the mammary gland, mammary gland cell proliferation, and immune system function.

The relationship between alcohol consumption and breast cancer risk will be better understood as more information about the interactions between alcohol and other risk factors becomes available and as additional insight into biological mechanisms is gained. The need to clarify this issue is a priority, since alcohol intake appears to be one of the few modifiable breast cancer risk factors yet identified (Hankinson and Willett 1995; Rosenberg et al. 1993).

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